REMARKS

Status of the Claims.

Claims 45-61 and 62-76 are pending in the application. Claims 45-61 and 68-76 were pending prior to this Amendment, claims 62-67 (and 77-86) having been cancelled in the Amendment filed on April 14, 2003 in response to the Final Rejection. Claims 62-67 are re-presented herein in light of the Examiner's indication of claims 45-67 as allowed. Claim 68 is amended herein. This amendment adds no new matter.

Election/Restriction Requirement.

Claims 45 and 68, the only pending independent claims, are Markush claims reciting multiple chromosomal regions. Earlier in prosecution, the Examiner identified these chromosomal regions as distinct species and required Applicants to elect one for initial examination. Applicants elected chromosomal region 17q22-q24, and the Examiner examined the claims with respect to this region.

Election of species practice relating to Markush claims is governed by M.P.E.P § 803.02, which states:

> This subsection deals with ***Markush-type generic claims*** which include a plurality of alternatively usable substances or members. In most cases, a recitation by enumeration is used because there is no appropriate or true generic language.

(Emphasis added.) Applicants respectfully point out that claims 45 and 68 are Markush-type generic claims that read on the elected species, chromosomal region 17q22-q24.

Section 803.02 states:

> ***Should applicant, in response to this rejection of the Markush-type claim, overcome the rejection***, as by amending the Markush-type claim to exclude the species anticipated or rendered obvious by the prior art, ***the amended Markush-type claim will be reexamined. The prior art search will be extended to the extent necessary to determine patentability of the Markush-type claim.***

(Emphasis added.) In the present application, in response to the rejection of Markush-type claims, Applicants have overcome an obviousness-type double patenting rejection by filing a Terminal Disclaimer and have overcome § 102 and § 103 rejection by pointing out that the references do not

teach or suggest an amplification at 17q22-24 (see below). Therefore, Markush-type claims 45 and 68 must be reexamined, and the prior art search must be extended to the extent necessary to determine the patentability of these claims. Applicants submit that § 803.02 requires the Examiner to examine at least one additional species recited in these claims. If the Examiner is able to make a proper art-based rejection of this additional species, the Examiner need not go on to examine any other species. If the Examiner is not able to make such a rejection, the Examiner must go on to examine another additional species. Examination of the Markush claims must continue until the Examiner encounters a species that can properly be rejected over prior art or the Markush claims are fully examined. Accordingly, Applicants respectfully request examination of one or more of the additional species recited in claims 45 and 68, in compliance with § 803.02.

35 U.S.C. § 102.

Claims 68, 69, 71, and 74 stand rejected under 35 U.S.C. § 102 as allegedly anticipated by Tsuda et al. (Cancer Research (1989) 49:3104-3108). Office Action, page 2. This rejection is respectfully traversed.

Of the rejected claims, only claim 68 is independent. Claim 68 relates to a "method for detecting a copy number variation in a suspected breast cancer sample by detecting a gain of an entire chromosome or chromosome arm or an amplification of unique sequences at" positions including q22-q24 on chromosome 17. Detection is carried out by hybridizing a suitable probe to the sample and detecting the hybridization complex.

The Examiner states: "Tsuda teaches [a] method for detecting a copy number variation in a suspected breast cancer sample . . . by detecting an amplification or gain of unique sequences . . . on chromosome 17, about position q22 to about position q24." Office Action, page 2. More specifically, the Examiner believes that Tsuda teaches the region "about position q22 to about position q24" because, according to the Examiner, Tsuda teaches that amplification "'of c-erbB2 was confirmed to be a factor indicating a poorer prognosis in breast carcinoma patients', also see figure 1, case A, where earl a position 17q21-22 is amplified." *Id.* The Examiner also cites page 3104, column 2, which states that "c-erbB-2 and on of the v-erbA-related genes, ear-1 are localized on chromosomes 17q21 and 17q21-22, respectively." *Id.*

Tsuda detected amplification of c-erbB-2 by using a c-erbB-2 probe to probe a slot blot of breast cancer tumor DNA. Tsuda, page 3105, col. 1. Tsuda's data therefore does not address

the location of the amplified c-erbB-2 sequences. Tsuda reported that c-erbB-2 was located at 17q21 based on the work of others (*see* Tsuda, page 3104, col. 2), which later proved incorrect. c-erbB-2 is actually located at 17q12, as indicated in Applicants' specification (page 26, line 22) and in Exhibit A. Exhibit A is a copy of a PDF file downloaded from the UCSC Genome Browser. The second line from the top shows the chromosome band, which in this case is 17q12. The fifth line from the top shows the location of the exons of the c-erbB-2 gene. This file makes it clear that c-erbB-2 is at 17q12, not 17q21. As the range "about 17q22 to about 17q24" does not encompass 17q12, the claimed method is clearly distinct from the detection of amplifications of c-erbB-2.

A second gene that Tsuda disclosed as being amplified in breast cancer is ear-1, which Tsuda stated is at 17q21-q22. To be more precise, ear-1 is located at 17q21.1, as evidenced by Exhibits B and C. Exhibit B is a copy of a PDF file downloaded from the UCSC Genome Browser. The second line from the top shows the chromosome band, which in this case is 17q21.1. Midway down the page is the location of the exons of a gene designated "M24898." Exhibit C, also from the UCSC browser, shows that M24898 is one of the designations of ear-1. Thus, ear-1 is located at 17q21.1. Applicants submit that "about 17q22 to about 17q24" clearly distinguishes "17q21.1." As Tsuda fails to teach this element of claim 68, Tsuda does not anticipate the claimed method. Claims 69, 71, and 74 depend from claim 68 and are therefore novel over Tsuda for at least the same reason.

35 U.S.C. § 103(a).

Alitalo and Hainsworth

Claims 68-71 and 74-76 were rejected under 35 U.S.C. § 103(a) as allegedly obvious in light of Alitalo (Proc. Natl. Acad. Sci. USA (1983) 80:1707-11) in view of Hainsworth *et al.* (Cancer Genet. Cytogenet. (1991) 53:205-18). Office Action, page 4. This rejection is respectfully traversed.

Of the rejected claims, only claim 68 is independent. As noted above, Claim 68 relates to a "method for detecting a copy number variation in a suspected breast cancer sample by detecting a gain of an entire chromosome or chromosome arm or an amplification of unique sequences at" positions including q22-q24 on chromosome 17.

The Examiner stated that "Alitalo teaches a method for detecting an amplification of 8q24 comprising contacting a chromosome sample with a labeled nucleic acid probe which binds to 8q24 . . . [and] detecting the hybridization complex." Office Action, page 4. The Examiner further stated: "Hainsworth teaches that, at least in some instances, there is chromosomal gain at 17q23 in primary breast cancers (see table 2, case 907, where there is a derivative of chromosome 17 which is translocated in 17q23, which represents an amplification at that position)." *Id.*

In the Amendment filed in response to the Final Office Action, Applicants argued that Hainsworth did not teach or suggest an amplification. In the Advisory Action, the Examiner accepted this argument, but nevertheless contended that the Hainsworth translocation represented a "gain" at the recited location. Advisory Action. The Examiner bases this view solely on Hainsworth's disclosure of a primary breast cancer case having a chromosome 17 abnormality denoted "der(17)t(17;?)(q23;?)." This "shorthand" would be interpreted by a cytogeneticist as describing a derivative of chromosome 17 that contained translocated chromosome 17 material joined to an unknown chromosome. The breakpoint on chromosome 17 is q23, and the chromosome 17 material is joined to an unknown point on the other chromosome. There is simply no basis for concluding that this description suggests an increase in copy number of nucleic acid sequences at q22-q24 on chromosome 17.

The rejection is based on an interpretation of the word "gain" to encompass a situation where there is no increase in the number of copies of unique sequences per genome, but rather a change in location of sequences. The Examiner contends that such a translocation represents a gain because the new location of the translocated material "gains" sequences." This interpretation of the word "gain" is not supported by the specification, which consistently uses this term to indicate an increase in sequence copy number per genome. *See, e.g.*, Applicants' specification, page 14, lines 18-20; page 23, lines 18-20; page 30, lines 18-21. The specification also uses the term "gain" to describe the presence of an additional entire chromosome or chromosome arm. *See, e.g.*, Applicants' specification, page 89, lines 10-17. This is a standard usage of the term "gain" in cytogenetics.

Although Applicants believe that the previous wording of the claim clearly excluded the detection of chromosomal abnormalities that were not accompanied by any variation in copy number per genome, Applicants have amended the claims in an effort to even more clearly recite the

invention. Accordingly, claim 68 recites: "A method for detecting a copy number variation in a suspected breast cancer sample by detecting a gain of an entire chromosome or chromosome arm or an amplification of unique sequences at at least one chromosomal region." Applicants submit that there is no evidence that case 907 in Hainsworth had "a gain of an entire chromosome or chromosome arm" or, as the Examiner concedes, "an amplification of unique sequences at at least one chromosomal region." Accordingly, the Alitalo-Hainsworth combination fails to teach or suggest all of the elements of claim 68. Claims 69-71 and 74-76 depend from claim 68 and are patentable over Hainsworth for at least this reason. Therefore, Applicants respectfully request withdrawal of the § 103 rejection of claims 68-71 and 74-76 over Alitalo and Hainsworth.

Tsuda and Mullis

Claims 70, 75, and 76 were rejected under 35 U.S.C. § 103(a) as allegedly obvious in light of Tsuda in view of Mullis *et al.* (U.S. Patent No. 4,683,202) Office Action, page 5. This rejection is respectfully traversed.

Claims 70, 75, and 76 depend from claim 68 and therefore incorporate the element of detecting an amplification at about 17q22 to about 17q24. The Examiner contends that Tsuda teaches the detection of amplifications in this region. However, as pointed out above, Tsuda teaches amplifications at 17q12 and 17q21.1, not at about 17q22 to about 17q24.

Mullis does nothing to remedy this deficiency. Mullis is cited as teaching the elements recited in claims 70, 75, and 76, namely labeling the sample nucleic acid (claim 70), using amplified DNA as the sample nucleic acid (claim 75), and using cDNA as the sample nucleic acid (claim 76). *See* Office Action, page 5. Mullis neither teaches nor suggests anything about detecting a copy number variation in a suspected breast cancer sample by detecting a gain of an entire chromosome or chromosome arm or an amplification of unique sequences at" positions including 17q22-q24, as recited in claim 68 and incorporated into dependent claims 70, 75, and 76. Thus, the Tsuda-Mullis combination fails to teach or suggest all of the elements of rejected claims 70, 75, and 76. Withdrawal of the § 103 rejection of these claims over Tsuda and Mullis is therefore respectfully requested.

Conclusion

In view of the foregoing, Applicants believe that all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (510) 769-3509.

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Respectfully submitted,

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